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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/749,119	12/30/2003	Richard L. Boyd	286336.152US1/NOR-013CP2	3286

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EXAMINER
LI, QIAN JANICE

ART UNIT	PAPER NUMBER
1633	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/749,119	BOYD, RICHARD L.	
	Examiner	Art Unit	
	Q. JANICE LI	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 February 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *19-26,28-40,42-44,46-49,53,55-64 and 66-75* is/are pending in the application.

4a) Of the above claim(s) *21, 22, 24, 26, 32, 33, 37, 44, 53, 56, 61, 63, 67, 71-75* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *19,20,23,25,28-31,34-36,38-40,42,43,46-49,55,57-60,62,64,66 and 68-70* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *30 December 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 2/3/09 has been entered.

The amendment and remarks filed 2/3/09 are acknowledged. Claims 19, 66, 69 have been amended. Claims 19-26, 28-40, 42-44, 46-49, 53, 55-64, 66-75 are pending, however, claims 21, 22, 24, 26, 32, 33, 37, 44, 53, 56, 61, 63, 67, 71-75 are withdrawn from further consideration by the Examiner, pursuant to 37 CFR 1.142(b), as being drawn to non-elected inventions, there being no allowable generic or linking claim. Claims 19, 20, 23, 25, 28-31, 34-36, 38-40, 42, 43, 46-49, 55, 57-60, 62, 64, 66, 68-70 are under current examination.

Unless otherwise indicated, previous rejections that have been rendered moot in view of the amendment to pending claims will not be reiterated. The arguments in 2/3/09 response would be addressed to the extent that they apply to current rejection.

Election/Restrictions

Applicant's election with traverse of Group I, is acknowledged. The elected invention is drawn to a method of inducing graft tolerance in a patient, and species

election drawn to a combination of the following: depleting T cells with chemotherapy before thymus reactivation in a post-puberty patient, reactivate thymus with leuprolide, and administering hematopoietic cells to inducing tolerance to an allogenic organ/tissue. Upon further consideration, group IV,(claims 69, 70) has been rejoined with group I, and the restriction between groups IV and I is hereby withdrawn. Claims 19, 20, 23, 25, 28-31, 34-36, 38-40, 42, 43, 46-49, 55, 57-60, 62, 64-66, 68-70 read on the elected invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 19, 20, 23, 25, 28-31, 34-36, 38-40, 42, 43, 46-49, 55, 57-60, 62, 64, 66, 68-70 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for increasing tolerance in a patient to a graft from a MHC-mismatched donor, wherein the graft is allogeneic hemopoietic or mesenchymal stem cells, does not reasonably provide enablement for increasing tolerance in a patient to a subsequent graft from the same MHC-mismatched donor, wherein the graft is not the stem cells. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims, for reasons of record and following.

The amended claims explicitly require administering stem and progenitor cells from a MHC-mismatched donor to a recipient, and *subsequently* administering another graft of the donor to the recipient.

In view of the teaching of the specification, it states in the abstract "The present disclosure provides methods for inducing tolerance in a recipient to a mismatched graft of an

organ, tissue and/or cells. By reactivating the recipient's thymus and providing hematopoietic stem cells from the donor, the previously "foreign" matter becomes recognized as "self" in the recipient and is not rejected". In working example I (§V), under the title "Castration Induces Tolerance to Allograft", the applicant contemplates, "The results will show that donor Balb/cJ skin transplanted onto a donor-reconstituted C57BL/6J mouse who has been castrated "takes" (i.e., is accepted) better than the donor skin transplanted onto a donor-reconstituted C57BU6J mouse who is sham-castrated, e.g., because the sham-castrated mouse does not have adequate uptake of donor HSC into the host thymus to produce DC. A donor skin graft is found not to take on a recipient, sham-castrated, C57BL/6J mouse who has not been reconstituted with Balb/cJ bone marrow" (Emphasis added). In example XIII, under the title of "Induction of Tolerance in Humans", the specification states, "The recipient patient will be monitored to detect the presence of donor blood and dendritic cells in his/her peripheral blood. When such donor cells are detected, the transplantation of the donor tissue (i.e., skin and/or organ) is made. The donor tissue is accepted by the recipient to a greater degree (i.e., survives longer in the recipient) than in a recipient who had not had his thymus reactivated and had not been reconstituted with donor CD34+ cells". In the specification, no data is provided actually showing that castrated mouse recipient takes the subsequent skin graft better than the sham-castrated recipient and does so in a statistically significant manner.

Turning to the state of the art, although it was well known in the art that transplantation of mesenchymal stem cells can reduce an immune response to a subsequent allogenic graft (e.g. *McIntosh et al*. UPS 6,368,636), the art of record also show castration has no effect on graft survival. As cited previously, *Takami et al* (J

Heart Lung Transplant 1995;14:529-36) teach orchiectomy (activating thymus through castration) had no influence on graft survival time or grade of rejection (e.g. the abstract); *Schofield et al* (J Heart Lung Transplant 2002;21:493-5) reported that the leuprolide hormone therapy appears to increase the risk of cardiac allograft rejection; *Antus et al* (Transpl Int 2002;15:494-501) teach testosterone treatment increases graft rejection while estrogens reduced the degree of graft rejection. It is particularly noteworthy that *Sykes et al* (US 2002/0159999) teach in the context of inducing graft tolerance the steps of immune suppression or T cell depletion, and administration of hematopoietic stem cells, while thymus is deactivated by radiation to "make space" for the stem cell transplantation. In view of the aforementioned knowledge in the art, it is incumbent upon the applicant to provide factual data to contradict the facts found in the references. However, the specification fails to provide any evidence beyond the prophetic teaching, and hence, the assertions in the specification remains in the realm of speculation.

Likewise, the claims are directed to using hematopoietic stem cells, epithelial stem cells, dendritic cells for inducing tolerance to a subsequent graft. However, the specification fails to establish and it was not known in the art that these particular stem cells are capable of inducing tolerance. In fact, it was known in the art that allogenic dendritic cells are often responsible for initiating graft rejection. For example, *Galkowska et al*. (Ann Transplant 1999;4:5-10) teaches skin allograft are acutely rejected despite of intensive immunosuppressive therapy. *Galkowska et al* demonstrated that circulating canine allogeneic dendritic cells facilitated recruitment of T lymphocytes into skin graft

and promote an extensive graft destruction compared to the less expressed effect of allogeneic mononuclear cells. In view of such, the claimed invention does not appear to be enabled in the absence of evidence to the contrary.

In the remarks, the applicant argues the anti-tumor response shown in the post-filing publication from the applicant is irrelevant because the tumor cells are not from the same donor of the allogenic HSC. The argument is persuasive, but the *Goldberg* publication still fail to support what is now claimed because the *Goldberg* publication reduced to practice showing that surgical castration promoted hematopoietic and T cell recovery following allogeneic HSC transplantation, and increased cell numbers in bone marrow and thymus. However, the *Goldberg* publication does not further test whether the castration would lead to tolerance to a subsequent graft from the same donor, and thus it fails to support the claims wherein the manipulation of steps a) to c) increased tolerance to a subsequent allogeneic graft of step d). The specification and the post-filing publication only support an enhanced recovery of the allogenic hematopoietic cells (of step c), not increased tolerance to another graft (instant step d).

Therefore, in view of the limited guidance, the lack of predictability of the art and the breadth of the claims, one skill in the art could not practice the invention without undue experimentation as it is broadly claimed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 19, 20, 23, 31, 34-36, 42, 43, 46, 55, 57-60, 62, 64, 66, 68-70 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over *McIntosh et al.* (USP 6,368,636), in view of the BBC News (December 1998) and *Jett et al*. (Breast Cancer Res Treat 1999;58:131-6).

McIntosh teaches a method for increasing tolerance to an allogeneic graft, the method comprises depleting T cells of a recipient by myeloablation (total body irradiation), infusion of mesenchymal stem cells, followed by implanting a bone marrow graft (e.g. example 8, particular column 17, 1st zpar), wherein the MSCs may come from the donor of the marrow graft (e.g. column 3, lines 12-22) and may be genetically modified (e.g. column 18). *McIntosh* reported allogeneic MSCs can support the rapid engraftment of bone marrow hematopoietic cells and there is no clinical evidence of GVHD and concludes "THE OPTION TO ENGRAFT ALLOGENEIC TISSUE BY USING ALLOGENEIC MSCS BROADENS THE RANGE OF TRANSPLANT MATERIAL USABLE IN CLINICAL TRANSPLANT SCENARIOS" (column 24, lines 36-39). *McIntosh* does not teach reactivating the thymus of the patient.

The cited BBC News supplemented the deficiency by establishing it was known in the art that chemical or surgical castration restore the youthful appearance of the thymus and T cell production to pre-pubertal levels, that the castration suppresses the production of sex hormones but could boost the immune system of transplant patients

who have been given immunosuppressive regimen (paragraphs 1-3, page 2). The cited BBC News does not specify using leuprolide for temporary castration.

Jett supplemented the deficiency by establish it was well known in the art that leuprolide is as effective as surgical castration (e.g. the abstract).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method taught by *McIntoch* by including the chemical or surgical castration in a transplantation protocol as taught by the BBC News for boosting recovery with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to do so for added benefit of restoring the recipient immune system such as in a complex clinical case, wherein additional measurement to ensure the success of stem cell transplantation is required. Although the combined teachings do not specify a kit, the LHRH antagonists were known in the art, it would have been obvious to the skilled in the art to assemble a kit containing active ingredients to be used in the combined therapy for the ease of commercial activity. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claims 25, 28, 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over *McIntosh et al.* (USP 6,368,636), in view of the BBC News (December 1998) and *Jett et al*. (Breast Cancer Res Treat 1999;58:131-6) as applied to claims 19, 20, 23, 31, 34-36, 42, 43, 46, 55, 57-60, 62, 64, 66, 68-70 above, further in view of *Allen et al.* (Cell Immunol 1997;181:127-38).

The combined teaching of *McIntosh* in view of the BBC News and *Jett* does not teach using hematopoietic stem cell for inducing graft tolerance.

Allen supplemented the deficiency by establishing it was well known in the art that implanting CD34+ hematopietic stem cells into thymus would induce prolonged tolerance to allogeneic graft and donor-derived skin grafts survived twice as long as third party grafts in unimmunosuppressed recipients (e.g. page 131-132, table 2).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method taught by *McIntosh* in view of the BBC News and *Jett* by intrathymus injection of CD34+ as taught by *Allen* in place of MSCs with a reasonable expectation of success. Given both methods of inducing tolerance were known in the art, it is within the knowledge of the skilled to determine which method to use in a given situation. Hence, the limitation falls within the bounds of experimental preference and optimization. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claims 38-40, 47-49 are rejected under 35 U.S.C. 103(a) as being unpatentable over *McIntosh et al.* (USP 6,368,636), in view of the BBC News (December 1998) and *Jett et al*. (Breast Cancer Res Treat 1999;58:131-6) as applied to claims 19, 20, 23, 31, 34-36, 42, 43, 46, 55, 57-60, 62, 64, 66, 68-70 above, further in view of *Mardiney III et al.* (USP 6,863,885).

The combined teaching of *McIntosh* in view of the BBC News and *Jett* does not specify using cytokines in hematopoietic stem cell transplantation.

Mardiney III supplemented the deficiency by establishing it was well known in the art to include certain cytokines and growth factors in a therapeutic regimen for promoting recovery after bone marrow transplantation. *Mardiney III* teaches a method for allogeneic graft comprising administering hematopoietic growth factors and cytokines, ablating the patient's T cells by non-myeloablative dose of radiation or chemotherapy, followed by hematopoietic stem cell transplantation. *Mardiney III* teaches the radiation eradicates diseased blood cells, while the growth factor promotes the regeneration of new blood cells (e.g. column 3 and claims).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method taught by *McIntosh* in view of the BBC News and *Jett* by including cytokines and growth factors in a transplantation protocol as taught by *Mardiney III* with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to do so for added benefit of restoring the recipient hemotopoietic system. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Response to Arguments

In the remarks, the applicant argues because the Office provided evidence in the rejection under 35 U.S.C. 112, 1st paragraph, that castration had no influence on graft survival, the art of record teaches away from the present invention and the skilled in the art would have no reasonable expectation of success.

The argument has been fully considered. The problem here is the specification fails to provide factual evidence to support the claimed invention and to contradict the art-known fact regarding castration, stem cell transplantation and a subsequent graft survival, and thus it fails to shade any new light on the matter. As such, if the applicant argues the art is unpredictable, then the specification fails to provide an enabling disclosure for what is now claimed because the prophetic teaching of the specification would be as unpredictable as the cited art.

On the other hand, the BBC News had made known of the applicant's finding before instant filing date, that castration restored thymus function and would be beneficial for transplantation patients undergoing immunosuppressive therapy. It would provide the motivation for the skilled in the art to combine the regimen in a transplantation protocol. The chance of success for the cited art is as good as instantly claimed.

Accordingly, for reasons of record and *supra*, the rejections are reasonable.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Q. Janice Li** whose telephone number is **571-272-0730**. The examiner can normally be reached on 9:30 am - 7 p.m., Monday through Friday, except every other Wednesday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joseph Woitach** can be reached on **571-272-0739**. The **fax** numbers for the organization where this application or proceeding is assigned are **571-273-8300**.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

For all other customer support, please call the USPTO Call Center (UCC) at **800-786-9199**.

/Q. JANICE LI/

Primary Examiner, Art Unit 1633